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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/101,825	07/17/98	GRONHOJ LARSEN C	GRONHOJ-LARS

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EXAMINER	
HAMUD, F	
ART UNIT	**PAPER NUMBER**
1647	18

DATE MAILED: 01/30/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	Examiner	Group Art Unit	19

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE THREE MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☒ Claim(s) 18-72 is/are pending in the application.

Of the above claim(s) 44 AND 57-60 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 18-31, 33-43, 45-56, AND 61-72 is/are rejected.

☒ Claim(s) 32 is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

The amendment filed October 2, 2000 has been received and entered into the record.

All 35 USC statutes not cited in this Office action can be found cited in full in a previous Office action.

In previous amendments claims 1 - 17 were canceled and claims 49 - 64 added in the amendment filed in Paper No. 8 on 12/21/99. Additionally, applicant's amendment filed 10/2/00 has added new claims 65 - 72. As explained on page 2 of the previous Office action, the examiner has rejoined elected Group I with Group II in view of applicant's persuasive traversal. Therefore, claims 18 - 72 are now pending in the case. Claims 44 and 57 - 60 remain withdrawn from consideration because they are directed to the non-elected invention.

Objections to the Specification Withdrawn

It is noted that applicant has appropriately inserted a sentence at the beginning of the disclosure to claim priority under 35 USC 120 by stating that the instant application is a 371 of PCT/DK97/00021.

It is further noted that applicant has amended the specification to include the appropriate figure legends in the "Brief Description of the Drawings"

It is also noted that applicant has added an abstract of the disclosure as required by 37 CFR 1.72(b). Applicant has also amended the specification in order to conform to required headings.

Withdrawal of 35 USC 101 Rejection

The previous rejection of claims 18 - 39, 48, and 55 under 35 USC 101 as reading on non-statutory subject matter found in nature has been withdrawn in view of applicant's amendment to claim 18 now requiring that the claimed polypeptide be "non-naturally occurring" and "about 100 amino acids in length. These new limitations now exclude the naturally occurring IL-10 polypeptide since it contains about 160 amino acids.

Withdrawal of 35 USC 102 Rejection

The previous rejection of claims 18 - 26, 48, and 55 as being anticipated by Vieira et al. has been withdrawn because the amendment to claim 18 excludes the naturally occurring IL-10. In addition, Vieira et al. fails to disclose fragments of IL-10.

Withdrawal of 35 USC 103 Rejections

Each of the previous obviousness rejections using Vieira et al. as the primary reference have been withdrawn because Vieira et al. fails to disclose fragment of IL-10 which are now excluded by the phrases "non-naturally occurring" and by "amounting in total up to about 100 amino acids".

Maintenance of Scope of Enablement Rejection

Claims 18 - 43, 45 - 56, 61 - 64, and new claims 65 - 72 are rejected under 35 USC § 112, first paragraph, as being enabling for claims directed to peptides having Seq ID Nos. 1 and 19 - 22 and for methods of treating pancreatitis using said peptides wherein the amino acid substitutions are limited to the naturally occurring amino acids (so long as this limitation does not constitute new matter). However, the above claims

are not enabled for any and all peptides encompassing the peptides defined by Seq. ID Nos. 1 and 19 - 22 nor for the litany of diseases specified in claim 56 for the reasons already of record on pages 4 - 9 of the Office action mailed March 30, 2000 and for the additional reasons presented below.

All non-naturally occurring amino acids is an infinite genus:

All of the current claims encompass peptides defined by the general formulae of Seq ID Nos. 1 and 19 - 22 wherein specific positions can be substituted by any conceivable amino acid, i.e., any non-naturally occurring amino acid. Furthermore, the additional amino acids which can increase the size of said peptide up to about 100 amino acids can also be of any sequence using any amino acid!

It is the **limitless breadth** of these claims combined with the **minimal guidance** in the specification for regarding which among all of the conceivable amino acids can be substituted or extended onto the hexapeptides and nonapeptdies of Seq ID Nos. 1 and 19 - 22 and the unpredictability of the effect of substituting or altering even a single amino acid in a protein that leads to the conclusion that it would require undue experimentation on the part of a skilled artisan to practice the full scope of the claimed invention.

The applicant first attempts to define the examiner's rejection as a mere recognition of the mathematical fact that there are a very large number of sequences of amino acids sequences from six up to about 100 amino acids that are encompassed by the variations in the claims. The applicant then cites In re Angstadt to support his position that the claims are, in fact, enabled. These arguments have been fully

considered but are not deemed persuasive.

Angstadt affirms the well accepted position that the applicant does not have to make and test every species within a claimed genus. Nor should applicant be limited to only his specific embodiments. However, Angstadt does not clearly define what is the appropriate genus around a specific number of embodiments. The question is whether the disclosure is commensurate in scope to the claim. The examiner maintains that the disclosure is not commensurate to the scope of the claims even if the claims are limited to Seq. ID Nos. 1 and 19 -22 having only additional amino acids added to the amino terminal portions of the molecule because the term "non-naturally occurring amino acid" encompasses thousands and even millions of different compounds.

The issue of enablement involves consideration of not only the breadth of the claims, which is in this case is enormous, but also of factors that include the amount of guidance provided by the specification, the degree of unpredictability in the art, and the quantity of experimentation required. In the instant case, the only adequate guidance provided by the disclosure is for the peptides defined by Seq. ID Nos. 1 and 19 -22 wherein the amino acid substitutions are naturally occurring amino acids (if this limitation fully supported by the specification) and for a method for treating pancreatitis using said peptides.

The situation where the claims begin to exceed reasonableness is the substitution of "any non-natural or unusual amino acid" into said peptides. Such a limitation encompasses thousands of various amino acids.

Similarly, the inclusion of any and all peptidomimetics modeled on the basis of the formula of SEQ ID NO. 19 far exceeds any adequate guidance in the disclosure. Such limitations moves the claimed invention into the realm into an invitation to experiment. The peptidomimetic linkages is only defined by function and not by specific structure. This would allow the applicant to capture all peptidomimetic structures ever discovered in the future! The specification is dramatically deficient in teaching which specific peptidomimetic linkages can be substituted for which specific peptide linkages in Seq ID Nos. 1 and 19 - 22 while retaining even one of the eleven different biological activities.

All possible amino acid sequences (up to about 100) that can be added upstream is also infinite.

While the applicant has now narrowed the claims to the C-terminal end of the IL-8, there remains a complete lack of guidance with regard to what specific amino acids and what specific amino acid sequences can be added to the N-terminal region of the non-peptides and not destroy the biological activity of the molecule. The applicant alleges that any natural or non-natural amino acid of any sequence up to about 100 amino acids can be appended to the active nonapeptide. This expansive definition apparently derives from the fact that the active nonapeptide resides at the C-terminal end of a polypeptide of 180 amino acids. However, it is well accept in the art of peptide chemistry that the biological effects of the substitution of even a single amino acid can great alter the tertiary structure of a protein thereby altering the biological activity. Without demonstrating the retention of biological activity of the nonapeptide appended

to wide divergent polypeptides to the N-amino end, the person of skill in the art would not find the applicant extrapolation to be scientifically reasonable and sound. Again in this instance, it is yet again an open invitation to experiment to find out what amino acid sequences up to about 90 amino acids can, in fact, be appended to the N-teminal part of the active nonapeptide without destroying the biological activities. The current use of combinatorial libraries in drug development does not obviate the applicant's burden of providing the necessary guidance of selecting amino acid sequences that can be appended to the active nonapeptide without adversely effecting the biological activities.

Once again, when taken as a whole, the excessive breath of the claims, the amount of experimentation required to practice the full scope of the claims, the unpredictability of the effects of adding up to 90 amino acids to the active peptide of any sequence of any natural or non-naturally oocurring amino acids, and the lack of guidance and working examples, the examiner reasonably concludes that it would require undue experiment on the part of the person of skill in the art to practice the full scope of this invention.

Method claims 49 - 54, 56, 61, 63 - 64, and 69 - 72 are only enabled for a method for treating pancreatitis using a peptide selected from the group consisting of Seq. ID Nos. 1 and 19 - 22 wherein the amino acid substitutions are limited to the naturally occurring amino acids. These method claims are first of all not enabled to their full scope for the same reasons provided above for the lack of full enablement for the peptides. Furthermore, the methods are only enabled for the treatment of pancreatitis and not any of the other diseases in the breath-taking list of

other diseases because the disclosure does not document that there is a specific correlation between the treament of an art accepted animal model of each disease and the successful treatment of said disease in humans. A blanket allegation that IL-10 is implicated in each of the claimed diseases is not adequate to enable treatment of each disease with any of an infinite number of peptides. There is no specific treatment dosages, mode of administration, or treatment regimen for each of the diseases encompassed by the majority of the claims. **Specifically, there are no dosages, mode of administration, or treatment regimen for the treatment or prevention of cancer, arthritis, ARDS-like syndrome, AIDS, pre-term labour caused by infectioin or other conditions, rheumatoid arthritis, gout, sepsis syndrome, hyperthermia, ulcerative colitis, enterocolitis, osteoporosis, cytomegalovirus, periodontal diseases, glomerulonephritis, chronic non-infectious inflammation of the lung, granuloma formation, fibrosis of the liver, transplant rejection, graft vs. host disease, chronic myeloid leukemia, acute myeloid leukemia, other neoplastic diseases, asthma bronchiale, diabetes mellitus, type I (insulin dependent), arteriosclerosis, atherosclerosis, psoriasis, chronic B lymphocyte leukemia, common variable immunodeficiency, side-effects from using other biological response modifiers, disseminate intravascular coagulation, systemic sclerosis, encephalomyelitis, lung inflammation, hyper IgE syndrome, cancer metastasis and growth, adoptive immune therapy, acquired respiratory distress syndrome, sepsis, reperfusion syndrome, postsurgical inflammation, organ transplantation,**

and alopecia. If even one of the claimed peptides could be used to treatment all of the above diseases, applicant would have an elixir for the gods. Clearly, given the breadth of the method claims, the lack of guidance for treatment other than for pancreatitis, the lack of working examples, and the high degree of unpredictability in treating such a vast array of different diseases, the person of skill in the art would be faced with an undeniable burden of undue experimentation to practice the full scope of the claimed methods.

The applicant argues that the "prevention of any disease" and especially pancreatitis is fully enabled by the instant specification. This argument has been fully considered but is not deemed persuasive. While the use of applicant's active peptide appears to reduce the seriousness of pancreatitis, there is no evidence in the disclosure that verifies that this treatment fully and completely cures pancreatitis. Without such a finding, there can be no reasonable claim to enabling a method for preventing pancreatitis.

Lack of Adequate Written Description

Claims 18 - 31, 33 - 43, 45 - 56, and 61 - 72 are rejected under 35 USC 112, first paragraph, for lacking an adequate written description that would clearly convey to the artisan that the applicant was in possession of the full scope of the claimed peptides and methods for preventing pancreatitis and for methods for treating or preventing any of the other litany diseases in claims 42, 44, and 56, at the time of filing the application.

The disclosure fails to define the common structural elements of this enormous genus of amino acids that would permit substitution for each specific naturally occurring amino acids without disrupting and/or destroying the biological activities of the peptides defined by Seq. ID Nos. 1 and 19 - 22.

The specification fails to describe what sequences (about 100 amino acids) can be added upstream to the active peptide(s) without disrupting or destroying the anti-inflammatory characteristics of said peptide, except for the sequence upstream in the naturally occurring IL-10. There is no description of which specific amino acids can be added in which of the 90+ positions upstream of the peptide without destroying biological activity.

There is no description of the method for preventing pancreatitis or for treating or preventing any of the numerous other diseases in claims 42, 44, and 54 that includes dosages, modes of administration, treatment regimen, etc.

In summary, it is apparent that the instant specification only adequately describes a peptide having the Seq ID Nos. 1 and 19 - 22 wherein the substitutions are limited to the naturally occurring amino acids or other limited unusual amino acids. Furthermore, the instant disclosure only adequately describe a method for treating pancreatitis with the said peptides.

Applicant's arguments against the scope of enablement rejection has been fully considered but are not deemed persuasive for the reasons given above.

Summary of claims:

Claim 32 is objected to but would be allowable if rewritten in independent form including all of the limitations of the independent claims and all intervening claims.

Claims 18 - 31, 33 - 43, 45 - 56, and 61 - 72 are rejected. All claims under consideration are free of prior art.

Any inquiry concerning this communication or earlier communications form the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, cna be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4277. Faxed draft or or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Gary L. Kunz

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